chemical interaction between the two materials.

Claim 18. (New) The process of claim 17 wherein microcrystalline cellulose is coprocessed with from about 0.1 to about 20% silicon dioxide, based on the amount of microcrystalline cellulose.

Claim 19. (New) The process of claim 17 wherein the coprocessing is performed by spray-drying.

REMARKS

Claims 1, 3-4, 6, 11, 14-19 are pending in the present application. Applicant has canceled claims 2, 5, 7-9, 12 and 13. At page 6, lines 12 - 19, the specification provides the basis for the amendments to claim 1. At page 4, lines 23 - 28, and page 7, lines 4 - 11, the specification provides the basis for new claims 15 and 16. At page 3, lines 20-23, the specification provides the basis for the for the amendments to claim 11 and for new claims 14, 17-19. Applicant has not raised any issue of new matter.

The specification has also been amended to correct a typographical error. All instances of the term "carmellose" have been replaced with "croscarmellose".

Rejection Under 35 U.S.C. 102(b)

Claims 1, 3-4, 6, and 11 stand rejected as being anticipated

by Posti '354 (US 5,525,354) under 35 U.S.C. 102(b). Applicants assert that the present invention is distinct from what is disclosed by Posti '354.

Posti '354 discloses a pharmaceutical preparation for oral use containing a pharmacologically acceptable salt of a dicholoromethylene biphosphonic acid (a clodronate) especially disodium clodronate. The preparation as disclosed in Posti '354 may also contain additives, such as carriers, diluents, filler, lubricants, and disintegrating agents. More specifically, Posti '354 uses microcrystalline cellulose (MCC) as a filler and colloidal silicon dioxide (SiO_2) as a lubricant. Example 1 of Posti '354 illustrates a tablet comprising disodium clodronate, microcrystalline cellulose and silicon dioxide.

Posti '354 Does NOT Contain Silicified Microcrystalline Cellulose

The Examiner states that the preparation according to Posti '354 "...also comprises of silicified microcrystalline cellulose..." and refers to Example 1 of the reference. Applicant asserts, however, that this is incorrect and points out that Example 1 of Posti '354 indicates that "...the clodronate-polyvidon-granules are mixed with the colloidal silicon dioxide, Croscacarmellose sodium and microcrystalline cellulose" (column 3, lines 23-25). Simply mixing colloidal SiO_2, Croscacarmellose sodium and MCC does NOT form the silicified microcrystalline cellulose (SMCC) of the present invention.

SMCC cannot be formed simply by copressing or mixing the

components of SiO_2 and MCC. This is especially so if the two components are part of a mixture comprising several other additives. Rather, the formation of SMCC requires the **coprocessing** of MCC and SiO_2. In practice, this is achieved, for instance, by spray-drying a suspension of MCC and SiO_2. This is clearly disclosed in the present application text as filed (see page 3, lines 20 - 28).

SiO_2 and MCC, as described in the present application, forms an agglomerate of the two components wherein SiO_2 and MCC are in intimate association with each other. This means that the SiO_2 has been integrated with the MCC particles, but there is no chemical interaction between the two materials. In a mixture with other components, the obtained SMCC acts as an individual, unitary component. Such a unitary SMCC component is not formed in any of the known granulation or tabletting techniques such as wet granulation, dry granulation, or direct compression of a mixture of SiO_2 and MCC.

Furthermore, when used in pharmaceutical preparations, MCC and SiO_2 are typically added to the tabletting mixture at different stages of the process and, consequently, both components are distributed independently among the other components of the mixture. It is not expected, to those skilled in the art, for SiO_2 to gather around the MCC during granulation or tabletting, let alone form SMCC, when the SiO_2 and MCC components are separately added.

Because of the reasons stated above, the pharmaceutical

preparation made in Posti '354 cannot and does not contain SMCC, thus making the present invention distinct from the pharmaceutical preparation of Posti '354.

Additionally, the Applicant has made some additional comparative tests in which clodronate tablets comprising SMCC are compared to clodronate tablets comprising MCC and colloidal SiO_2. The results of these tests are shown in the Rule 1.132 Declaration enclosed herewith. The enclosed Declaration was properly executed by Dr. Juhani Posti - the first named inventor of the Posti '354 reference being cited against the present application.

The enclosed Declaration shows the advantageous properties of tablets made with SMCC compared to tablets made with a mixture of MCC and SiO_2. Among other noteable results, the Examiner should take note that the friability of the tablets made with MCC and SiO_2 is not acceptable under current pharmacopoeial requirements, whereas the the tablets made with SMCC had superior results. These comparative tests clearly demonstrate that 1) SMCC does not form during granulation or tabletting and 2) SMCC provides advantages and unexpected results over the separate addition of MCC and SiO_2.

For the reasons stated above and the results shown in the enclosed Declaration, Applicant asserts that the present invention is indeed distinct from that disclosed in Posti '354. Applicant respectfully requests that the rejections made under 35 U.S.C. §102(b) be withdrawn.

Rejection Under 35 U.S.C 103(a)

Claims 1, 3-4, 6, and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Posti '354 (US 552,354). Applicant asserts that the present invention is not obvious in light of Posti '354 and the current rejection should be withdrawn.

The Examiner states that it would be obvious to one of ordinary skill in the art, at the time of invention, by routine experimentation, to omit the water and/or ethanol from the preparation in order to achieve the applicant's goal of dry granulation because the reference teaches the preparation is carried out using known granulating techniques and dry granulation is well known in the art. The Examiner further states that the expected result would be a pharmaceutical preparation containing the active ingredient disodium clodronate with silicon dioxide and microcrytalline cellulose and lubricants and/or disintegrating agents in order to provide an oral solid dosage form compressed into a tablet.

The Examiner must present a *prima facie* case of obviousness consisting of references describing each element of the claimed invention and motivation or suggestion to modify or combine the references such that one of ordinary skill in the art had a reasonable expectation of success of making the present composition. Applicants point out to the Examiner that 1) Posti '354 does not describe or suggest the SMCC element of the

presently claimed invention, 2) there is no motivation to modify the Posti '354 reference to use SMCC instead of a mixture of MCC and SiO_2 to make the present composition of a clodronate tablet made with SMCC, and 3) there is no reasonable expectation to successfully make the tablet of the present invention containing SMCC simply by omitting water and/or ethanol from the preparation. As stated earlier, coprocessing MCC and SiO_2 effective to form SMCC is not a matter of simply omitting water and/or ethanol from the preparation.

The Examiner must realize that a mixture of MCC and SiO_2 is not the same as the SMCC used in the present invention. Because Posti '354 1) fails to disclose or suggest a pharmaceutical preparation made with SMCC rather than MCC and SiO_2 and 2) fails to show reasonable expectation of success in creating the tablet of the present invention with SMCC, the Examiner fails to establish *prima facie* obviousness of the invention. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. §103(a) rejection.

Furthermore, even if *prima facie* obviousness of the invention is deemed established, Applicants submit that the unexpected results shown in the Posti declaration, described above, demonstrate unobviousness of the invention. This is an additional reason to withdraw the instant rejection.

Extension of Time

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), the Applicants respectfully petitions for a two (2) months extension of time for filing a response in connection with the present application and the required fee of $400.00 is enclosed herewith.

If the Examiner has any questions regarding the above matters, please contact Applicants' representative, Gerald M. Murphy, Jr., at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____ #36,623
Gerald M. Murphy, Jr., #28,977

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/DRN/CAV

Enclosures: Version With Markings Showing Changes Made
Declaration Under 37 C.F.R. §1.132

VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Specification

Please replace the paragraph beginning on page 6, line 25, with the following replacement paragraph:

--Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	205 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 7, line 23, with the following replacement paragraph:

--Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	155 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 8, line 6, with the following replacement paragraph:

--Tablets were prepared with the following composition per

tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	155 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 8, line 21, with the following replacement paragraph:

--Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	140 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 9, line 6, with the following replacement paragraph:

--Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	125 mg

[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 9, line 20, with the following replacement paragraph:

--Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	132 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 10, line 3, with the following replacement paragraph:

--Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	165 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

Please replace the paragraph beginning on page 11, line 1, with

the following replacement paragraph:

--Disodium clodronate tetrahydrate 1000 mg responding

anhydrous disodium clodronate	800 mg
Microcrystalline cellulose (Emcocel 50 M)	132 mg
[Carmellose] Croscarmellose sodium	22 mg
Stearic Acid	15 mg
Magnesium stearate	8 mg--

In the Claims

Claim 1. (Amended) A tablet form of a pharmaceutical [Pharmaceutical] preparation comprising,

[containing as an active agent] 50 - 90% of a pharmacologically acceptable salt of dicholoromethylene biphosphonic acid as an active agent, and

[, characterized in that it is an oral solid dosage form comprising] and 5 - 25% silicified microcrystalline cellulose.

Claim 3. (Amended) The preparation [Preparation] according to claim 1, comprising: [characterized in that it comprises]

a) from about 60 to 80% by weight of anhydrous disodium clodronate;

b) from about 8 to 20% by weight of silicified microcrystalline cellulose; and

c) from about 0.5 to 10% by weight of lubricants and/or disintegrants.

Claim 4. (Amended) The preparation [Preparation] according

to claim 1 or 3 [any one of the preceding claims] wherein silicon dioxide is present in the silicified microcrystalline cellulose in an amount of from about 0.1 to 20% weight, based on the weight of the microcrystalline cellulose.

Claim 6. (Amended) The preparation [Preparation] according to claim 1 or 3, wherein [any one of the preceding claims, characterized in that] the salt of dichloromethylene biphosphonic acid is the disodium salt.

Claim 11. (Amended) A pharmaceutical preparation, comprising,

a pharmaceutically [pharmaceutical] acceptable salt of dicholoromethylene biphosphonic acid, and

an excipient, said excipient comprising silicified microcrystalline cellulose obtained by coprocessing microcrystalline cellulose with from about 0.1 to about 20% silicon dioxide, based on the amount of microcrystalline cellulose[.], to form an agglomerate of microcrystalline cellulose and silicon dioxide wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other and the silicon dioxide is integrated with the microcrystalline cellulose particles, but there is no chemical interaction between the two materials.